REMARKS

This application is a 371 filing of PCT International application no. PCT/EP2003/012129 filed October 31, 2003. Claims 13-17 remain pending in the application.

Claim 13 is amended above to clarify that the autoantibodies used in the detection method claimed by Applicants are labeled polyclonal human autoantibodies against the TSH receptor that have been obtained by affinity purification using TSHr.

Rejection under 35 U.S.C. §102

Claims 13-17 are rejected under 35 U.S.C. §102(b) as being anticipated by Parmentier et al. According to the Office Action, Parmentier et al. teach that the antibody used in the method to detect TSH receptor is purified polyclonal autoantibody against TSH receptor from serum of patients with Graves' Disease (GD). The Office Action maintains that Applicants' recitation of "affinity purified polyclonal human autoantibodies" amounts to a product-by-process limitation that does not distinguish over Parmentier et al., and that Parmentier et al., therefore anticipates the claims of the present application. Applicants respectfully disagree.

According to the Office Action, "...Parmentier teaches the antibody used in the method to detect TSH receptor is purified polyclonal autoantibody against TSH receptor from serum of patients with Graves' disease..." Beginning at column 14, line 51, Parmentier et al. discloses a proof-of-concept experiment to demonstrate that cloned human TSHr can be used to assay for anti-TSHr autoantibodies. The assay disclosed by Parmentier et al., however, differs from the claimed method in two respects: 1) Parmentier et al. measures the displacement of radio-labeled TSH (^{125}I-TSH) from the receptor by patient autoantibodies, not, as in the claimed method, the displacement of autoantibodies by autoantibodies; 2) Parmentier et al. teaches that the autoantibodies were obtained from patient sera by ammonium sulfate *fractionation* of the patient sera. Parmentier's immunoglobulin preparation, unlike Applicants', was not further purified (see table below comparing Applicants' claimed method with that of Parmentier et al.)

Prior Art Comparison Table

	Parmentier et al.	**Brown et al.**	**Applicant**
What is being measured	displacement of ^{125}I-TSH by patient autoantibodies	displacement of ^{125}I-TSH by IgG from normal individuals	displacement of patient autoantibodies by patient autoantibodies
Competition for hTSHr between	^{125}I-TSH and immunoglobulins from GD patients	^{125}I-TSH and immunoglobulins from normal individuals	patient autoantibodies and patient autoantibodies
Preparation of antibodies	ammonium sulfate precipitation of patient sera followed by dialysis	ammonium sulfate precipitation of normal sera followed by thyroid membrane purification	affinity purified using TSHr-affinity column
Purification of antibodies	*no purification* crude preparation of immunoglobulins/non-specific	*membrane* affinity-purified/not TSHr specific	*TSHr* affinity-purified/TSHr specific

Contrary to the Office's position that Applicants' recitation of "affinity purified polyclonal human autoantibodies amounts to a product by process limitation that does not distinguish over Parmentier et al., Applicants point out that ammonium sulfate precipitation is a simple and effective means of *fractionating* proteins. It is based on the fact that at high salt concentrations the natural tendency of proteins not to aggregate is overcome, since the surface charges are neutralized. Charge neutralization means that proteins will tend to bind together, form large complexes and hence are easy to precipitate out by mild centrifugation. Since each protein will start to aggregate at a characteristic salt concentration, this approach provides a simple way of *enriching* for particular proteins in a mixture, and is used, for example, to isolate immunoglobulins from sera.

As one of skill in the art would recognize, ammonium sulfate fractionation, is generally employed as the initial step in the isolation of crude antibodies from serum. "Salting out" of polypeptides occurs at high salt concentrations where the salt competes with the polar side chains of the protein for ion pairing with the water molecules, and where the salt reduces the effective volume of solvent. As expected from these observations, the amount of ammonium sulfate required to precipitate a given protein will depend mainly on the surface charge, the surface distribution of polar side chains, and the size of the polypeptide, as well as the pH and

temperature of the solution. Immunoglobulins, as a group, precipitate at 40–50% ammonium sulfate saturation depending somewhat on the species and subclass.

Ammonium sulfate fractionation results in a crude preparation of immunoglobulin, not a purified antigen-specific antibody as used in the method as claimed above.

Antigen specific affinity purification, on the other hand, as known to those of skill in the art and as described at pages 17-19 of Applicants' specification provides antibodies that are, as the name implies, purified based on their antigen specificity. Applicants' specification details the preparation of a TSHr affinity column with which the anti-TSHr autoantibodies in the patient sera are purified.

Accordingly, Parmentier et al. fails to teach or fairly suggest two features of the claimed method and therefore, cannot anticipate Applicants' claimed method. Withdrawal of the rejection under 35 U.S.C. §102 is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 13-17 are rejected under 35 U.S.C. §103(a) as being unpatentable over Parmentier et al. in view of Brown et al.

The teaching of Parmentier et al. is discussed above.

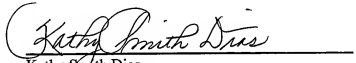
Brown et al. teaches the presence of an IgG component of normal serum that inhibits binding of TSH to thyroid membranes, not TSHr. Brown et al. extract IgG from the sera of normal individuals by ammonium sulfate precipitation (page 157, first column, first ¶.) This crude Ig preparation is subsequently *partially* purified (see title) by incubation with thyroid membranes (page 157, col. 1, 3rd ¶.) Brown et al. then use the membrane purified antibody preparation to competitively inhibit binding of labeled bovine TSH to *thyroid membranes*. Like Parmentier et al., competition for binding of the receptor is between TSH and the autoantibodies.

Thus, Brown et al., like Parmentier et al. fails to teach or suggest 1) antigen specific affinity purification of anti-TSHr autoantibodies or 2) their use in a competitive method for the detection of anti-TSHr autoantibodies in a patient sample; Brown et al. therefore, cannot compensate for the deficiencies in the teachings of Parmentier et al. Like Parmentier et al., there is no teaching or suggestion in either reference from which one of skill would conclude that antigen-specific affinity purified patient-derived autoantibodies would be useful in a competition assay to measure the amount of like autoantibodies in a biological sample.

Withdrawal of the rejection of claims 13-17 under 35 U.S.C. §103 is respectfully requested.

It is respectfully submitted that the above-identified application is now in condition for allowance and favorable reconsideration and prompt allowance of these claims are respectfully requested. Should the Examiner believe that anything further is desirable in order to place the application in better condition for allowance, she is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,



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